REMARKS

Claims 45-54 are pending. Applicants make these amendments without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject mattered. Support for these amendments appears throughout the specification and claims as filed. No new matter is introduced by these amendments.

Rejection under 35 U.S.C. § 103(a)

Claims 45-54 are rejected as unpatentable over Herron (US Patent 4,764,521) in view of Rubenstein (IDS, CJ) and Rephaeli et al. (US Patent 5,939,455). Applicants traverse.

Applicants acknowledge the assertion in the Action regarding discussion of the references individually, however, wish to also note that the comments on any single reference bears on the overall teaching of the combination of references. More particularly, that equivocal teachings of a cited reference in a combination may also put into question the veracity of the combination and thus impact the teaching or suggestion that one of ordinary skill in the art would, in fact, glean from such combination.

Applicants also wish to note that the claims relate to unsaturated, 4-carbon chain-containing compounds for use in treating cystic fibrosis in a mammal.

It is stated is in the Action that Herron generally teaches that substituted carboxylic acids are known to be useful for treating respiratory disease, including cystic fibrosis. While acknowledging that Herron does not teach Applicants' unsubstituted compound subject matter, it is further asserted in the Action that the teachings of Rubenstein and Rephaeli (both to unsubstituted aryl carboxylic acids) bridges the gap between Herron and Applicants' claimed subject matter. Applicants traverse.

First, Herron does not definitively teach that Herron's compounds are useful in treating cystic fibrosis. A closer inspection of Herron shows that Herron: (i) describes their compounds as leukotriene antagonists (at col. 1, lines 18-22); (ii) notes that leukotrienes have been reported in sputum of cystic fibrosis patients (at col. 17, lines 47-51); (iii) postulates that this finding "suggests" a role of leukotrienes in cystic fibrosis (at col. 17, lines 52-53); and (iv) then concludes that the Herron compounds "should" also alleviate some of the symptoms of cystic fibrosis by virtue of their leukotriene antagonizing ability (at col. 17, lines 59-63). The combination of (i) to (iv) above incorporates much speculation and fails to provide a reasonable basis for concluding with any degree of certainty that Herron teaches compounds useful in treating cystic fibrosis. Thus, Applicants traverse the assertion that Herron, in fact, teaches compounds that are established as useful in treating cystic fibrosis.

Rubenstein teaches one compound, 4-phenylbutyric acid, for treatment of cystic fibrosis. The Rubenstein compound is specifically excluded from Applicants' pending claims. Rubenstein, neither alone or in combination, provides any mention regarding Applicants' Δ3-trans-butenoic acid compound. The Rubenstein 4-phenylbutyric acid compound has a fully saturated hydrocarbon chain linking the acid and phenyl moieties. This is distinct and distinguishable from Applicants' Δ3-trans-butenoic acid compound, which has an unsaturated hydrocarbon chain. The physicochemical (including atom orbital geometry (i.e., sp2 v sp3 hybridization), three-dimensional spatial orientation, and thus functional properties (e.g. biological activity) and therapeutic properties of compounds having the carbon-carbon single bond (i.e., Rubenstein compound) are distinct and distinguishable from compounds having the carbon-carbon double bond (i.e., Applicants' claimed subject matter). Rubenstein does not indicate any particular correlation between functional group moiety and cystic fibrosis activity of their compound, and on this basis Applicants submit that Rubenstein does not teach or suggest to one of ordinary skill in the art that Applicants' claimed carbon-carbon double bond containing compounds would

necessarily be useful in treating cystic fibrosis. It is only Applicants' disclosure in their instant specification that provides such teaching.

Rephaeli is asserted in the Action to teach "a variety of butyric acid derivatives." However, similarly to Rubenstein, Applicants submit that Rephaeli fails to teach or suggest unsaturated, 4-carbon chain-containing compounds as claimed by Applicants. None of the cited compounds in Rephaeli exemplifies unsaturated, 4-carbon chain-containing compounds of Applicants' claims.

Applicants reiterate that their claimed subject matter has unexpectedly superior activity relative to cited art compounds cinnamic acid and 4-PBA. Exhibit A (previously submitted) is an autoradiograph showing ΔF508-CFTR protein expression in model cells of cystic fibrosis treated with the indicated compounds. ΔF508-CFTR is present in two bands, B and C. Band B corresponds to the immature core-glycosylated isoform of CFTR; Band C corresponds to the mature complex-glycosylated CFTR isoform. ΔF508-CFTR Bands Band C were quantitated by densitometry, and the quantitation is shown in Exhibit B (previously submitted). Cells treated with trans-SAA produced increased amounts of both the immature and the mature forms of ΔF508-CFTR, consistent with an increase in CFTR production. These results indicate that trans-SAA is surprisingly effective in promoting the trafficking of functional ΔF508-CFTR to the cell surface relative to cinnamic acid and 4-PBA. Applicants therefore submit that their instantly claimed subject matter is not rendered obvious in view of the cited art and respectfully request withdrawal of the rejection.

It is also asserted in the Action that claims 45-54 are obvious in view of Faller et al. (WO 99/40883). Applicants traverse. Faller lists a number of compounds. However, similarly to Rubenstein and Rephaeli, Applicants submit that Faller fails to teach or suggest unsaturated, 4-carbon chain-containing compounds as claimed by Applicants.

Applicants submit that Herron, Rubenstein, and Rephaeli, in combination, and Faller alone, fail to teach or suggest the desireability of Applicants claimed subject matter. The teaching of Herron is equivocal as applied to cystic fibrosis and combined with Rubenstein and Rephaeli, which both lack a teaching of Applicants' unsaturated, 4-carbon chain-containing compounds, does not teach or suggest Applicants' unsaturated, 4-carbon chain-containing compounds for use in treating cystic fibrosis.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call Applicants' undersigned representative to discuss the application. Applicants thank the Examiner in advance for this courtesy.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. (71699) 49632.

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Respectfully submitted,

By_____

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